D4

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 May 2002 (23.05.2002)

PCT

(10) International Publication Number
WO 02/40013 A1

(51) International Patent Classification[7]: A61K 31/22, 38/40, A61P 9/10, 5/06, 31/04, 31/12, 37/04, 43/00 // A61K 38/40, 31:22

(21) International Application Number: PCT/IT01/00395

(22) International Filing Date: 24 July 2001 (24.07.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
RM2000A000601
17 November 2000 (17.11.2000) IT

(71) Applicant *(for all designated States except US)*: **SIGMA-TAU HEALTHSCIENCE S.P.A.** [IT/IT]; Via Treviso, 4, I-00040 Pomezia (IT).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: **POLA, Pietro** [IT/IT]; Via delle Ortensie, 35, I-00040 Rocca di Papa RM (IT).

(74) Agents: **CAVATTONI, Fabio** et al.; Cavattoni - Raimondi, Viale dei Parioli, 160, I-00197 Roma (IT).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/40013 A1

(54) Title: COMPOSITION FOR STIMULATING THE IMMUNE DEFENCE AND IRON METABOLISM, CONTAINING PROPIONYL L-CARNITINE AND LACTOFERRIN

(57) Abstract: A composition is disclosed which can be used as a health food/dietary supplement or as a drug for the prevention and/or treatment of peroxidative lipid disorders, of myocardial and cerebral disorders and of abnormalities of iron metabolism and for regulating and stimulating the immune defences, containing as its characterising components propionyl L-carnitine and lactoferrin or a natural product containing lactoferrin.

COMPOSITION FOR STIMULATING THE IMMUNE DEFENCE AND IRON METABOLISM, CONTAINING PROPIONYL L-CARNITINE AND LACTOFERRIN

The present invention relates to a composition suitable for the prevention and/or treatment of peroxidative lipid disorders such as atherosclerosis, of myocardial and cerebral distress, of abnormalities related to iron metabolism and growth factor disorders, of bacterial and viral infections and of forms of cell degeneration. The composition is also suitable for regulating and stimulating the immune defences.

Accordingly, the composition may take the form and exert the activity of an actual medicine, depending upon the support or preventive action or the strictly therapeutic action that the composition is intended to exert according to the particular individuals in whom it is to be used.

More particularly, the composition according to the invention contains as its characterising ingredients:

(a) propionyl L-carnitine or one of its pharmacologically acceptable salts; and

(b) lactoferrin or a natural product containing lactoferrin such as whey or colostrum, or mixture thereof.

The metabolic action both of L-carnitine and of the alkanoyl L-carnitines such as acetyl L-carnitine, propionyl L-carnitine, isovaleryl L-carnitine and butyryl L-carnitine is well known. Their function, in fact, is very important for the production of energy, which takes place mainly through the intramitochondrial β-oxidation of fatty acids, the oxidation of branched-chain amino acids and the regulation of insulin activity. Also important is their protective activity against peroxidative phenomena which has been observed both at cerebral level and at myocardial and renal endothelial level.

Another important property is their ability to stabilise cellular phospholipid membranes and the deformability of erythrocytes as well as the stimulation of erythropoietic activity.

All these biological activities account for the favourable effects obtained by the administration of "carnitines" (a term used to denote collectively both L-carnitine and the above-mentioned alkanoyl L-carnitines) in many pathological conditions depending above all on an energy production defect or on lipid peroxidation phenomena such as are encountered in myocardial insufficiency, vascular and cerebral disorders and in prolonged physical exercise.

Lactoferrin, too, like the "carnitines", has a particular physiological role in the body, not only in the regulation of iron metabolism, but also in many mechanisms underlying the immune responses and operating against bacterial and viral infections.

Lactoferrin, which is regarded as belonging to the transferrin group, is a glycoprotein formed by 703 amino acids which is isolated both from cow's milk and human milk, and is above all present in high percentages in colostrum. As well as being present in milk, lactoferrin is also present in plasma, derived from neutrophils, in seminal fluid, in the mucous membranes, in tears and in sweat.

Colostrum, i.e. the mother's milk secreted immediately after childbirth, is particularly rich in lactoferrin, which constitutes 20% of the total proteins present in colostrum.

The high lactoferrin content in colostrum is due to the fact that the immune defences in the newborn are weak and it is precisely lactoferrin that provides the organic defences. To this end it is important that it should not be degradable by tryptic enzymes and that it is well absorbed

by the stomach.

In organic fluids lactoferrin is present as a monoferric, diferric or iron-free structure.

Three isoferrins of lactoferrin have been isolated, two of which, i.e. lactoferrin-beta and lactoferrin-gamma, with RNase activity, and one, lactoferrin-alpha, without RNase activity.

Specific receptors for lactoferrin have been identified in intestinal tissue, in macrophages and monocytes, in neutrophils, in platelets and in certain bacteria.

The antibacterial activity of lactoferrin is related above all to its ability to bind to iron and therefore to prevent the growth of those bacteria which need iron for their proliferation. In addition to its effect on bacterial growth, a further antibacterial action of lactoferrin has been demonstrated, caused by incorporation of lactoferrin in the bacterial membrane and consequent dispersion of the lipopolysaccharides of the bacterial wall with permanent alterations of its permeability. Lactoferrin, moreover, is capable of exerting an antifungal and antiviral effect, as well as of exerting an inhibiting effect on the growth of many forms of tumours and of regulating and enhancing the immune defences, especially when these are depressed or insufficient.

Other known properties of lactoferrin are its antioxidant ability, its inhibition of platelet aggregation and of the formation of thrombi, and its anticholesterolaemic activity.

It has now surprisingly been found that a composition containing as its characterising components a combination of:

(a) propionyl L-carnitine or one of its pharmacologically acceptable salts; and
(b) lactoferrin or a natural product containing lactoferrin, selected from the group consisting of whey, colostrom or mixture thereof,
is extremely effective in the prevention and treatment of peroxidative lipid disorders such as atherosclerosis, of myocardial and cerebral distress, of abnormalities related to disorders of iron metabolism and growth factors, of bacterial and viral infections and forms of cell degeneration, and is also suitable for regulating and stimulating the immune defences owing to the potent synergistic effect exerted by its components.

The composition may also contain an additional "carnitine" selected from the group consisting of L-carnitine, acetyl L-carnitine, butyryl L-carnitine, valeryl L-carnitine and isovaleryl L-carnitine or their pharmacologically acceptable salts or mixtures thereof.

The weight-to-weight ratio of component (a) to component (b) ranges from 1:0.1 to 1:10, and preferably from 1:0.5 to 1:2.

Here below are described a number of the most significant tests confirming the unexpected, potent synergistic effect exerted by the combination according to the invention described herein.

Tests on oxidant effects induced by H_2O_2

For these tests a culture of pheochromocytoma cells (PC-12) containing 3 $\times 10^5$ M cells/mL was used, which, according to the procedure described by Nordman (Nordman R., Free Rad. Biol. Med., 1227, 1996), was subjected for 30 minutes to a solution of H_2O_2 0.1 mM.

At the start of the test, to the cell culture were added 100 μg/cc of lactoferrin or the same amount of propionyl L-carnitine or the two compounds in combination. After 24 hours, survival of the cells incubated with H_2O_2 alone was observed or survival of cells which, in addition to H_2O_2, were incubated with lactoferrin alone or propionyl L-carnitine alone or with the two compounds in combination.

It could be noted that, as a result of the peroxidation induced by H_2O_2, the cell survival was 30%, while the survival rates were 42% and 34% when the cells were incubated with H_2O_2 and lactoferrin and with H_2O_2 and propionyl L-carnitine, respectively.

Surprisingly, the cell survival rate increased to 90% when lactoferrin was given in combination with propionyl L-carnitine, thus demonstrating the potent synergistic effect of the above-mentioned compounds in protecting the cells against peroxidative damage induced by H_2O_2.

Tests on the immunosuppressive and toxic effects induced by mitomycin C

Intraperitoneal injections of mitomycin C in mice (50 μg/mouse/day) for five consecutive days caused substantial leukopenia, which in approximately 12 days led to the deaths of all the animals thus treated. The results of this test also revealed the potent synergistic effect exerted by lactoferrin and propionyl L-carnitine in protecting animals treated with mitomycin C against the lowering of the number of leukocytes and the mortality induced by mitomycin.

In fact, the oral administration of the combination of lactoferrin (20 mg/mouse) and propionyl L-carnitine (30 mg/mouse) from the first day of administration of mitomycin for five consecutive days, led to an above 70% survival rate in the animals thus treated compared to controls, as well as to a much more limited reduction in the number of leukocytes.

By contrast, the protective effect exerted by lactoferrin alone was only modest (survival: approximately 30%) as was that exerted by propionyl L-carnitine alone (survival: 15%).

The results of these tests are given in Tables 1 and 2 here below.

Table 1

Leukopenia in mice treated with mitomycin C after administration of lactoferrin and propionyl L-carnitine

Treatment	No. leukocytes after		
	5 days	10 days	12 days
Mitomycin C	5,600±360	3,100±290	1,300±260
Lactoferrin	5,900±280	5,000±380	4,600±390
Propionyl L-carnitine	6,100±320	4,200±405	4,300±425
Lactoferrin + propionyl L-carnitine	7,000±420	6,200±410	6,000±425

Table 2

Survival in mice treated with mitomycin C after administration of lactoferrin and propionyl L-carnitine

Treatment	% animals surviving after		
	5 days	10 days	12 days
Mitomycin C	60	30	10
Lactoferrin	75	45	30
Propionyl L-carnitine	70	30	20
Lactoferrin + propionyl L-carnitine	90	80	75

Some non-limiting examples of combination compositions according to the present invention are given hereinbelow:

1)	Propionyl L-carnitine	300	mg
	Lactoferrin	300	mg

2)	Propionyl L-carnitine	100	mg
	Acetyl L-carnitine	100	mg
	L-carnitine	100	mg
	Lactoferrin	300	mg
3)	Propionyl L-carnitine	300	mg
	Bovine colostrum	300	mg
4)	Propionyl L-carnitine	100	mg
	Acetyl L-carnitine	100	mg
	L-carnitine	100	mg
	Bovine colostrum	300	mg
5)	Propionyl L-carnitine	300	mg
	Lactoferrin	200	mg
	Vit. C	50	mg
	β-carotene	2	mg
	Pyridoxine	5	mg
	Folic acid	50	μg
	Vit. B_{12}	25	μg
	Vit. PP	25	μg
6)	Propionyl L-carnitine	75	mg
	Acetyl L-carnitine	75	mg
	L-carnitine	75	mg
	Butyryl L-carnitine	75	mg
	Lactoferrin	200	mg
	Colostrum	200	mg
	Lysine	100	mg
	Vit. C	50	mg
	Coenzyme Q_{10}	25	mg
	Pyridoxine	5	mg

What is meant by a pharmacologically acceptable salt of the various aforesaid carnitines mentioned in the present specification is, in addition

to the respective "inner salts", any salt of these with an acid which does not give rise to unwanted toxic or side effects. These acids are well known to pharmacologists and to experts in pharmaceutical technology.

Non-limiting examples of such salts are the following: chloride; bromide; iodide; aspartate, acid aspartate; citrate, acid citrate; tartrate; phosphate, acid phosphate; fumarate; acid fumarate; glycerophosphate; glucose phosphate; lactate; maleate; acid maleate; mucate; orotate; oxalate, acid oxalate; sulphate, acid sulphate; trichloroacetate; trifluoroacetate and methane sulphonate.

Among these salts, L-carnitine acid fumarate (US 4,602,039), acetyl L-carnitine mucate, propionyl L-carnitine mucate (US 5,952,379) and isovaleryl L-carnitine acid fumarate (US 5,227,518) are particularly preferred.

A list of FDA-approved pharmacologically acceptable acids is given in Int. J. Pharm., 33, 1986, 201-217, the latter publication being incorporated in the present specification by reference.

The supplement of the invention may further comprise vitamins, coenzymes, mineral substances, aminoacids and antioxidants. The supplement may be manufactured in the form of tablets, lozenges, capsules, pills, granulates, syrups, herb teas, vials or drops.

Claims

1. A combination composition comprising:
(a) propionyl L-carnitine or a pharmacologically acceptable salt thereof; and
(b) lactoferrin or natural product comprising lactoferrin selected from the group consisting of whey, colostrum or mixture thereof.

2. The composition of claims 1 wherein component (a), further comprises a "carnitine" selected from the group comprising L-carnitine, acetyl L-carnitine, butyryl L-carnitine, valeryl L-carnitine and isovaleryl L-carnitine or the pharmacologically acceptable salts or mixtures thereof.

3. The composition of claims 1 and 2 wherein the weight ratio (a):(b) ranges from 1:0.1 to 1:10, preferably from 1:0.5 to 1:2

4. The composition of anyone of the preceding claims which further comprises vitamins, sugars, coenzymes, mineral substances, aminoacids, peptides and antioxidants.

5. The composition of anyone of the preceding claims wherein the pharmacologically acceptable salt is selected from the group comprising: chloride; bromide; iodide; aspartate, acid aspartate; citrate, acid citrate; tartrate; phosphate, acid phosphate; fumarate; acid fumarate; glycero-phosphate; glucose phosphate; lactate; maleate; acid maleate; mucate; orotate; oxalate; acid oxalate; sulphate, acid sulphate; trichloroacetate; trifluoroacetate and methane sulphonate.

6. The composition of any of the preceding claims, orally administrable, in the form of a health food or dietary supplement.

7. The composition of anyone of claims 1-5, orally, parenterally, rectally, sublingually or transdermally administrable, in the form of a medicament.

8. The health food or dietary supplement of claim 6 manufactured as a solid, semisolid or liquid preparation.

9. The health food or dietary supplement of claim 8 manufactured as tablets, capsules, lozenges, pills, granulates, syrups or drops.

10. The health food of claim 9 in unit dosage form, which comprises:

Propionyl L-carnitine	300	mg
Lactoferrin	300	mg

11. The health food of claim 9 in unit dosage form, which comprises:

Propionyl L-carnitine	100	mg
Acetyl L-carnitine	100	mg
L-carnitine	100	mg
Lactoferrin	300	mg

12. The health food of claim 9 in unit dosage form, which comprises:

Propionyl L-carnitine	300	mg
Bovine colostrum	300	mg

13. The health food of claim 9 in unit dosage form, which comprises:

Propionyl L-carnitine	100	mg
Acetyl L-carnitine	100	mg
L-carnitine	100	mg
Bovine colostrum	300	mg

14. The health food of claim 9 in unit dosage form, which comprises:

Propionyl L-carnitine	300	mg
Lactoferrin	200	mg
Vit. C	50	mg
β-carotene	2	mg
Pyridoxine	5	mg
Folic acid	50	μg
Vit. B_{12}	25	μg
Vit. PP	25	μg

15. The health food of claim 9 in unit dosage form, which comprises:

Propionyl L-carnitine	75	mg
Acetyl L-carnitine	75	mg
L-carnitine	75	mg
Butyryl L-carnitine	75	mg
Lactoferrin	200	mg
Colostrum	200	mg
Lysine	100	mg
Vit. C	50	mg
Coenzyme Q_{10}	25	mg
Pyridoxine	5	mg

16. A therapeutic method for the prevention and/or treatment of peroxidative lipid disorders, such as atherosclerosis, myocardial and cerebral disorders, abnormalities related to iron metabolism and growth factor disorders, bacterial and viral infections and cell degeneration and for regulating and stimulating the immune difenses which comprises administering to an individual in need thereof a combination composition comprising the following ingredients:

(a) propionyl L-carnitine or a pharmacologically acceptable salt thereof; and

(b) lactoferrin or natural product comprising lactoferrin selected from the group consisting of whey, colostrum or mixture thereof.

17. The therapeutical method according to claim 16, wherein the component (a) further comprises a "carnitine" selected from the group comprising L-carnitine, acetyl L-carnitine, butyryl L-carnitine, valeryl L-carnitine and isovaleryl L-carnitine or the pharmacologically acceptable salts or mixtures thereof.

18. The therapeutical method according to claims 16 or 17, wherein, in said composition, the weight ratio (a):(b) ranges from 1:0.1 to 1:10, preferably from 1:0.5 to 1:2

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/IT 01/00395

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/22 A61K38/40 A61P9/10 A61P5/06 A61P31/04
A61P31/12 A61P37/04 A61P43/00 //(A61K38/40,31:22)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, EPO-Internal, PAJ, BIOSIS, MEDLINE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KERNER J ET AL: "A STUDY OF THE ACYLCARNITINE CONTENT OF SOWS'COLOSTRUM, MILK AND NEWBORN PIGLET TISSUES;DEMONSTRATION OF HIGH AMOUNTS OF ISOVALERYL-CARNITINE IN COLOSTRUM AND MILK" JOURNAL OF NUTRITION, WISTAR INSTITUTE OF ANATOMY AND BIOLOGY, PHILADELPHIA, PA,, US, vol. 114, no. 5, 1984, pages 854-861, XP002061795 ISSN: 0022-3166 table 2 --- -/--	1,2,4, 6-8

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 November 2001	03/12/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Böhmerova, E

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IT 01/00395

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	COFFEY M T ET AL: "CARNITINE STATUS AND LIPID UTILIZATION IN NEONATAL PIGLETS FED DIETS LOW IN CARNITINE 1, 2, 3" JOURNAL OF NUTRITION, WISTAR INSTITUTE OF ANATOMY AND BIOLOGY, PHILADELPHIA, PA,, US, vol. 121, no. 7, 1991, pages 1047-1053, XP002061794 ISSN: 0022-3166 abstract page 1048, left-hand column, paragraph 1 ---	1-18
Y	WO 98 01128 A (MENDES SRL ;SIMONE CLAUDIO DE (IT)) 15 January 1998 (1998-01-15) claims 1,2 ---	1-18
Y	ORLANDI A ET AL: "Propionyl-L-carnitine exerts a specific control on serum triglyceride levels and plaque progression in hypercholesteremic aged rabbits" AGE, AMERICAN AGING ASSOCIATION, CHESTER, PA, US, vol. 16, no. 3, July 1993 (1993-07), page 117 XP002101595 ISSN: 0161-9152 abstract ---	1-18
Y	PAULSON D J ET AL: "PROTECTION OF THE ISCHAEMIC MYOCARDIUM BY L-PROPIONYLCARNITINE: EFFECTS ON THE RECOVERY OF CARDIAC OUTPUT AFTER ISCHAEMIA AND REPERFUSION, CANITINE TRANSPORT, AND FATTY ACID OXIDATION" CARDIOVASCULAR RESEARCH, XX, XX, vol. 20, no. 7, 1986, pages 536-541, XP002042649 ISSN: 0008-6363 abstract ---	1-18
Y	KAJIKAWA MIKIO ET AL: "Lactoferrin inhibits cholesterol accumulation in macrophages mediated by acetylated or oxidized low-density lipoproteins." BIOCHIMICA ET BIOPHYSICA ACTA, vol. 1213, no. 1, 1994, pages 82-90, XP001036905 ISSN: 0006-3002 abstract --- -/--	1-18

INTERNATIONAL SEARCH REPORT

Int onal Application No
PCT/IT 01/00395

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	FILLEBEEN CARINE ET AL: "Lactoferrin is synthesized by mouse brain tissue and its expression is enhanced after MPTP treatment." MOLECULAR BRAIN RESEARCH, vol. 72, no. 2, 1 October 1999 (1999-10-01), pages 183-194, XP001022494 ISSN: 0169-328X page 191, right-hand column, paragraph 4 page 192, left-hand column, paragraph 3 -right-hand column, paragraph 2 ---	1-18
Y	KAWAKAMI H ET AL: "EFFECT OF LACTOFERRIN ON IRON SOLUBILITY UNDER NEUTRAL CONDITIONS" BIOSCIENCE BIOTECHNOLOGY BIOCHEMISTRY, JAPAN SOC. FOR BIOSCIENCE, BIOTECHNOLOGY AND AGROCHEM. TOKYO, JP, vol. 57, no. 8, 1993, pages 1376-1377, XP002035374 ISSN: 0916-8451 abstract ---	1-18
Y	IKEDA M ET AL: "LACTOFERRIN MARKEDLY INHIBITS HEPATITIS C VIRUS INFECTION IN CULTURED HUMAN HEPATOCYTES" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, ACADEMIC PRESS INC. ORLANDO, FL, US, vol. 245, 1998, pages 549-553, XP002923168 ISSN: 0006-291X abstract ---	1-18
Y	EP 0 753 308 A (GAMBIT INTERNATIONAL LIMITED) 15 January 1997 (1997-01-15) claim 1 ---	1-18
Y	EP 0 559 425 A (JAPAN IMMUNO INC) 8 September 1993 (1993-09-08) claim 1 -----	1-18

INTERNATIONAL SEARCH REPORT

formation on patent family members

Int ional Application No
PCT/IT 01/00395

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9801128 A	15-01-1998	IT RM960479 A1	05-01-1998
		CA 2260145 A1	15-01-1998
		EP 0909171 A1	21-04-1999
		WO 9801128 A1	15-01-1998
		JP 2000514437 T	31-10-2000
		US 6037373 A	14-03-2000
		US 6166077 A	26-12-2000
EP 0753308 A	15-01-1997	IT RM950473 A1	13-01-1997
		CA 2180689 A1	13-01-1997
		EP 0753308 A2	15-01-1997
		US 5834424 A	10-11-1998
EP 0559425 A	08-09-1993	JP 6316529 A	15-11-1994
		CA 2090658 A1	03-09-1993
		DE 69322896 D1	18-02-1999
		DE 69322896 T2	27-05-1999
		DK 559425 T3	30-08-1999
		EP 0559425 A1	08-09-1993
		US 5576299 A	19-11-1996